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REMARKS

I. Status of the Claims

Claims 1-11, 13-26 are currently pending. Claims 12, 27-47 were withdrawn by the Examiner from consideration on their merits for allegedly being directed to non-elected species. Claims 7, 8, 11, 13, 14, 15, and 21 are amended merely to clarify antecedent basis or correct typographic errors. No new matter has been introduced into the application as a result of the present amendments. Applicants gratefully acknowledge Examiner's decision that claims 15, 17 and 18 are otherwise allowable, aside from their dependency on currently rejected claims. However, the Applicants respectfully submit that the remaining claims are also allowable as discussed below.

II. Priority claim

The Examiner asserted that the Applicants have not complied with one or more conditions for receiving the benefit of the provisional application 60/408662 (the '662 application) under 35 U.S.C. §120, because the '662 application allegedly fails to provide adequate support or enablement consistent with the first paragraph of 35 U.S.C §112 for claims 1-3 of the instant application. The Examiner seems to assert that the '662 application only cites an example where all reagents were added simultaneously. The Examiner also asserted that the '662 application makes reference only to PKC, PKA, and Lck as specific transferases that can be used in the invention. The Applicants respectfully disagree.

The specification of the '662 application provides ample examples where the reagent for the kinase transferase reaction and reagent for luciferase reaction are added sequentially. *See.* for example, paragraphs [0015], [0034], [0034], [0043], [0045], [0047], and [0049]. In one example, the kinase reaction was allowed to proceed for 90 minutes, and then the reagent for the second step luciferase assay, the CellTiter-Glo Reagent (Promega, Catalog # G7570), was added. See paragraph [0043]. This commercial reagent includes a transferase quenching agent and was previously described for use in detecting viable cells. See Assignee Promega's earlier published international application WO 02/066671, published August 29, 2002 (a copy of this reference was included in

Applicants' Fifth Supplemental Information Disclosure Statement filed October 27, 2006), was prior to the filing date of Applicants' '662 application. Addition of the quenching agent is not a separate "necessary step" as asserted by the Examiner, but rather, the quenching agent is included in the reagent for the second step as disclosed in the '662 application.

Additionally, the specification provides ample teachings regarding the general applicability of the invention in measuring transferase enzymatic activity, particularly protein kinases including serine/threonine kinases, tyrosine kinases, and lipid kinases. See the '662 application at paragraph [0041]. Thus, a person of ordinary skill in the art would understand from the disclosure of the '662 application that the present invention is applicable to kinases generally including tyrosine kinases recited in pending claims 7-11. The examples in the '662 application provide representative examples of transferase enzymes.

Accordingly, the Applicants respectfully submit that the '662 application provides adequate support or enablement consistent with the first paragraph of 35 U.S.C §112 to all the pending claims in this application and thus the present application is entitled to the benefit of the prior-filed '662 application.

III. Objection to the Specification

The Examiner objected to the specification for containing a hyperlink. The Applicants submit that current amendments have rendered the objection moot.

IV. Objections to the Claims

The Examiner objected to claims 7, 8, and 14 for allegedly containing improper antecedent basis, and further objected to claim 16 for allegedly being of improper dependent form. The Applicants submit that current amendments have rendered the objections moot.

V. Claim Rejection under 35 U.S.C. § 112 Second Paragraph

Claims 11 and 21 stand rejected under 35 U.S.C §112 second paragraph for allegedly being indefinite. The Applicants submit that current amendments have rendered the rejections moot.

VI. Claim Rejection under 35 U.S.C. § 102 (e) based on Crouch

Claims 1-8, 19-20 and 22-26 are rejected under 35 U.S.C. § 102 (e) as allegedly being anticipated by Crouch et al. (U.S. Patent App. No. US2004/0253658A1, "Crouch") Specifically, the Examiner asserted that Crouch teaches a method of detecting kinase activity, wherein the kinase reaction can be allowed to proceed for a certain amount of time before the addition of luciferase and luciferin. The Examiner also asserted that Crouch teaches the advantage of first stopping the kinase reaction with a stopping solution before adding luciferase/luciferin. Applicants respectfully traverse the rejection.

As a threshold matter, the Federal Circuit has stated that for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. Corning Glass Works v. Sumitomo Electric, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. Connell v. Sears, Roebuck & Co., 220 U.S.P.Q 193, 1098 (Fed. Cir. 1983). Contrary to the Examiner's position, Crouch does not anticipate the claimed invention.

The present invention, as claimed, is directed to bioluminescence-based methods for measuring transferase enzymatic activity. After initiating a transferase action, a single reagent is then added to the transferase reaction mixture which quenches the transferase reaction and initiates the bioluminescence reaction in one step. The single reagent includes a bioluminescence-generating enzyme, a luminogenic molecule and transferase quenching agent which selectively stops transferase activity without substantially affecting bioluminescent enzyme activity. See present claims 1-3.

Crouch relates to a method for measuring protein kinase activity which involves (a) providing a first solution of ATP and protein kinase and a second solution of ATP (control); (b) adding a kinase substrate to the first and second solutions to form reaction mixtures; and (c) measuring ATP or ADP concentration or the rate of change with time

based on a bioluminescence reaction. See Abstract of Crouch. A separate stop reagent of phosphoric acid or metal chelators, if used at all, is added to the reaction mixture in step (b') to stop the reaction of the kinase prior to initiation of the bioluminescence reaction. See paragraph [0069]. The use of a separate stop reagent or solution requires extra steps to be performed prior to initiating the bioluminescence reaction. See Crouch's Example 1 and paragraph [0102]. See also claims 53 and 55 of Crouch. There is no disclosure or suggestion in Crouch of a method that employs a single reagent which simultaneously stops the kinase reaction and initiates the bioluminescence reaction as presently claimed. Thus, Crouch is not prior art against the independent claims 1-3, nor is it prior art against dependent claims 4-8, 19-20, and 22-26. Accordingly, Applicants respectfully request reconsideration and Withdrawal of the rejection of claims 1-8, 19-20 and 22-26 under 35 U.S.C. § 102 (e) in view of Crouch is in order and is respectfully requested.

VII. Claim Rejections under 35 U.S.C. § 103(a)

a. Claim rejection under 35 U.S.C. § 103(a) over Crouch

Claims 1-8, 19-26 are rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Crouch. Specifically, the Examiner asserted that Crouch teaches staurosporine being an effective kinase inhibitor, and it would have been obvious to one skilled in the art to use staurosporine as a stopping agent in a method of studying kinase activity with luciferase/luciferin described by Crouch. Applicants respectfully traverse the rejection.

The Federal Circuit reiterated the manner in which obviousness rejections are to be reviewed. Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, "a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1485 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). Contrary to the Examiner's position, the Applicants submit that Crouch, alone or

in combination with any of the references cited below, does not teach or suggest what the Applicants have done.

As discussed above, Crouch relates to a method of detecting transferase activity where the transferase activity is first stopped by adding a stop solution in step (b'), before the bioluminescence reaction is initiated. See Crouch at paragraph [0069]. Crouch does not teach a method where the transferase activity is quenched and the luminescence reaction is initiated simultaneously in one step. In fact, Crouch teaches away from the claimed invention by emphasizing the advantage of the separate step (b'), because "it allows one to make up and store large numbers of samples prior to testing." See Crouch at paragraphs [0069] to [0072]. Thus, it would not have been obvious to an ordinary skilled artisan, based on Crouch's teachings, to provide a method where the transferase activity is quenched and the luminescence reaction is initiated simultaneously in one step. According, the Applicants respectfully submit that the rejection under U.S.C. §103(a) of claims 1-8, and 19-26 based on Crouch is improper and should be withdrawn.

b. Claim rejection under 35 U.S.C. § 103(a) over Crouch in view of Briggs

Claims 1-10, 19-20, and 22-26 stand rejected as allegedly being obvious over Crouch in view of Briggs et al. (Biochem, 39:489-495, 2000, "Briggs") Specifically, the Examiner asserted that Crouch extends the application of its method to all kinases, and Briggs discloses the tyrosine kinases Src, Lck, Fyn, and Lyn. The Examiner further asserted that it would have been obvious to one skilled in the art to use Src family kinases described by Briggs in a method described by Crouch. Applicants respectfully traverse the rejection.

As discussed above, Crouch does not teach a bioluminescence-based method of detecting a transferase activity where the transferase activity is quenched and the luminescence reaction is initiated in one step. Briggs adds nothing to Crouch that could remedy the deficient teachings in Crouch. Briggs merely relates to additional tyrosine kinase family members. A disclosure of tyrosine kinase family members is not a teaching or suggestion of a method that employs a reagent that simultaneously quenches a transferase reaction and initiates the bioluminescence enzyme reaction as recited in the present claims. The cited art, either alone or in combination, does not teach or suggest

the present claims. Accordingly, the Applicants respectfully submit that the rejection under 35 U.S.C. §103(a) based on the combination of Crouch and Briggs is improper and should be withdrawn.

c. Claim rejection under 35 U.S.C. § 103(a) over Crouch in view of Lev

Claims 1-8, 11, 19-20 and 22-26 stand rejected as allegedly being obvious over Crouch in view of Lev et al. (EMBO J., 10:647-654, 1991, "Lev") Specifically, the Examiner asserted that Lev discloses receptor tyrosine kinases EGFR, PDGFR, and c-KIT. Examiner alleged that it would have been obvious to one skilled in the art to use growth factor receptor family tyrosine kinases disclosed in Lev in a method described by Crouch, because Crouch allegedly extends the application of its method to all kinases. Applicants respectfully traverse the rejection based on all the above assertions.

As discussed above, Crouch does not teach a bioluminescence-based method of detecting a transferase activity where the transferase activity is quenched and the luminescence reaction is initiated in one step. Lev adds nothing to Crouch that could remedy the deficiency in Crouch's teachings. Lev merely relates to additional tyrosine kinase family members. A disclosure of tyrosine kinase family members is not a teaching or suggestion of a method that employs a reagent that simultaneously quenches a transferase reaction and initiates the bioluminescence enzyme reaction as recited in the present claims. The cited art, either alone or in combination, does not teach all elements of the claim. Accordingly, the Applicants respectfully submit that the rejection under 35 U.S.C. §103(a) based on the combination of Crouch and Lev is improper and should be withdrawn.

d. Claim rejection under 35 U.S.C. § 103(a) over Crouch in view of Simpson

The Examiner further rejected Claims 1-8, 13-14, 16, 19-20, and 22-26 as allegedly being obvious over Crouch in view of Simpson et al. (J. Biolum. and Chemilum, 6:97-106, 1991, "Simpson") Specifically, the Examiner asserted that Simpson studied the effects of various types of detergents on the kinetics of the luciferase/luciferin reaction. The Examiner alleged that it would have been obvious to one skilled in the art to use a secondary solution comprising luciferin, luciferase and a

detergent in a method of detecting transferase activity as described by Crouch. Applicants respectfully traverse the rejection.

Contrary to the Examiner's position, what Simpson showed at best was that different types of detergents on a bioluminescence reaction had variable effects. Some types of detergent inhibit, whereas other types of detergent might stimulate luciferase activity. See Table 1 of Simpson. Simpson admitted that the effect of stimulation, if any, is only observed over a narrow range of detergent concentrations. See page 102, left column, first paragraph. Even among detergents that appear to stimulate luciferase activity, the alleged stimulation is mitigated by the fact that some detergents also irreversibly destabilize and inactivate the luciferase enzyme. For example, on page 102, left column, Simpson states:

> Cationic detergents also bring about decay in the light output of firefly luciferase reactions. This decay appears to be brought about by inactivation of the luciferase enzyme by the cationic detergent, since addition of ATP, D-luciferin or magnesium ions failed to restore activity. Under the conditions used in the present experiments, the inactivation was not reversible.

See also Table 1 and Figure 2 in Simpson. Additionally, Simpson showed that prior contact of detergents with luciferase enzyme in reagent preparation results in irreversible inactivation and reduction of luciferase activity. See Simpson at page 102, left column, first paragraph and Figure 5.

The Examiner also asserted that Simpson points out the possibility of adding a detergent to a luciferase reaction solution. However, the mere possibility would not have motivated one of skill in the art to do so, because Simpson also pointed out that, for unknown reasons, different luciferase preparations respond differently to the detergents. See Simpson at page 103, right column. In fact, Simpson cautioned against the use of detergent, especially non-ionic detergents, in a luciferase/luciferin solution due to the unpredictable effect of detergent on luciferase activity. See, for example, on page 103, right column, it states in part the following: "Clearly, in the light of the variability experienced, supplementation of firefly luciferase preparations with non-ionic detergents is not currently a viable proposition."

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Finally, the claimed invention is directed to bioluminescence-based methods of detecting a transferase activity where a reagent comprises a transferase quenching agent that stops the transferase activity without substantially affecting bioluminescent enzyme activity. Even if Simpson had shown any feasibility of adding a detergent in a luciferase/luciferin solution, neither Crouch nor Simpson, alone or in combination, teach or suggest the use of the detergent to simultaneously stop a transferase reaction and initiate a bioluminescence reaction. Withdrawal of the rejection of claims 1-8, 13-14, 16, 19-20, and 22-26 under 35 U.S.C. §103(a) over Crouch in view of Simpson is in order and is respectfully requested.

VIII. Conclusion

The Applicants believe that the application is ready for allowance. A favorable decision is earnestly solicited. If the Examiner has any question, he is invited to call the undersigned attorney at 312-913-2126.

Respectfully submitted,

Dated: November 14, 2006

Emily Miao
Reg. No. 35,285

McDonnell Boehnen
Hulbert & Berghoff, LLP
300 South Wacker Drive
Chicago, IL 60606
Telephone: 312-913-0001
Facsimile: 312-913-0002